Biochemical Urine Testing of Adherence to Cardiovascular Medications Reveals High Rates of Nonadherence in People Attending Their Annual Review for Type 2 Diabetes

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OBJECTIVE

Liquid chromatography—tandem mass spectrometry (LC-MS/MS) is a new method to objectively and robustly detect nonadherence. We applied this technique to study nonadherence to cardiovascular medications in people with type 2 diabetes (T2DM).

RESEARCH DESIGN AND METHODS

Routine urine samples, received at the time of the annual diabetes review from 228 people with T2DM in primary care, were assessed for adherence by LC-MS/MS.

RESULTS

A total of 28.1% patients (*N* = 64) were nonadherent to antidiabetic, antihypertensive, and/or lipid-lowering medications. Nonadherence to statins was the highest at 23.7%, and nonadherence to oral hypoglycemic agents was 9.3%. HbA_{1c}, albumin-to-creatinine ratio, and lipid profiles were significantly higher in the patients who were nonadherent compared with those who were adherent to treatment.

CONCLUSIONS

This unique study shows that routine urine samples can be used for adherence testing screening by LC-MS/MS and has demonstrated high nonadherence rates especially to statins in people with T2DM. Future intervention studies using LC-MS/MS as a diagnostic/therapeutic tool may help to improve clinical outcomes.

Cardiovascular disease is a major cause of morbidity and mortality in people with type 2 diabetes (T2DM) and is the largest contributor to health care costs in this population (1). Although the management of risk factors such as blood pressure, dyslipidemia, and glucose leads to legacy benefits of reduced microvascular and macrovascular complications (2), up to one-third of people with T2DM fail to derive optimal benefit from therapy because of nonadherence to medication (3). Further, poor adherence is associated with increased mortality and number of hospital admissions (4). Few reliable and practical tools exist to accurately to detect nonadherence to therapy (5).

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We have set up a unique and robust biochemical method using liquid chromatography—tandem mass spectrometry (LC-MS/MS) that can detect 60 of the most common cardiovascular medications in a spot urine sample (6). LC-MS/MS is an extremely specific and sensitive instrument with a detection limit in the low-nanogram range.

Medications are detected in the urine for between four and six half-lives of the drug, thus providing a snapshot of adherence in a patient (7). The aim of this unique study was to assess nonadherence in people with T2DM in the primary care setting using screening of urine samples by LC-MS/MS.

RESEARCH DESIGN AND METHODS

Population

The study was conducted from March 2016 to July 2017 and included all consecutive people with T2DM attending six different primary care practices in Leicestershire county of the U.K. for their annual diabetes review who consented to participate in the study. On the day of their routine diabetes review, patients were asked for verbal consent to participate in the study. In patients who consented, urine samples were analyzed for treatment adherence. Demographic information and biochemical data were retrieved retrospectively from the laboratory database while data on prescribed medications were collected from the patients' prescription lists.

Prior to attending the annual review, participants routinely provide a urine sample for albumin-to-creatinine ratio (ACR) analysis. Aliquots from these urine ACR samples received by the laboratory at the University Hospitals of Leicester National Health Service (NHS) Trust were stored at −80°C. Samples were analyzed, where suitable, using an Agilent Technologies (Santa Clara, CA) 1290 high-performance liquid chromatography system interfaced with an Agilent Technologies 6400 Series Triple Quadrupole LC/MS System, as described previously (6).

Total nonadherence was defined as the complete absence of any prescribed cardiovascular medications, partial nonadherence as the detection of at least one but not all cardiovascular medications, and total adherence as the detection of all the prescribed cardiovascular medications. The cardiovascular medications analyzed include 40 of the most common antihypertensive agents, oral hypoglycemic agents (OHAs), and oral lipid-lowering therapies.

The project met all governance and ethical requirements and was approved by the University Hospitals of Leicester NHS Trust as a quality improvement project (Registration #7766e).

Statistical Analysis

Data are presented as counts/percentages, medians with interquartile ranges, or means and SDs. Analysis of the associations between ACR; HbA_{1c}; lipid profile (total cholesterol [TC], LDL cholesterol, HDL cholesterol [HDL-C], TC/HDL ratio); and nonadherence to antidiabetic, antihypertensive, and lipid-lowering medications was conducted using ANCOVA with ACR, HbA_{1c}, and lipid profile as variables, and age (continuous variable), sex, and therapeutic nonadherence (binary phenotypes) as independent parameters. Analysis of the level of glycemic control was conducted using a Pearson χ^2 analysis with an HbA_{1c} level of <7% as a marker of adequate control without controlling for medications other than OHAs a priori. Similarly, the analysis of lipid control was conducted with TC of <5 mmol/L as a marker of adequate control without controlling for nonlipid medications a priori. All analyses were performed using SPSS version 24.

RESULTS

The clinical and biochemical characteristics of patients are shown in Table 1. Overall, of the total of 228 participants with suitable samples, 64 patients (28.1%) were completely or partially nonadherent to antidiabetic, antihypertensive, and/or lipid-lowering medications (labeled as "any nonadherent" in Table 1). Of these, 13 of 228 patients (5.7%) were not taking any of the prescribed cardiovascular medications (labeled as "total nonadherent" in Table 1) while the remainder of the 64 patients (i.e., 51 of 228 patients; 22.4%) were partially nonadherent to cardiovascular medications.

The highest rate of nonadherence in this cohort was for statins (42 of 177 analyzed drugs [23.7%]), while nonadherence to antidiabetic medications was 9.3% (N = 28 of 300 analyzed drugs) (Supplementary Fig. 1). After adjusting for age and sex, the means of ACR, HbA_{1c}, and lipid profiles were statistically higher for any nonadherent patients compared with adherent patients (Table 1). This difference was even more striking when comparing the total nonadherent group to the total adherent group.

Overall, 96 adherent patients (58.9%) and 28 of any nonadherent patients (44.4%) had an HbA_{1c} level of <7% (odds ratio 1.79 [95% CI 1.00–3.22]; P = 0.050), suggesting better glycemic control in adherent patients. Similarly, 155 adherent patients (95.1%) and 45 of any nonadherent patients (75.0%) had TC levels of <5 mmol/L (odds ratio 6.45 [95% CI 2.57–16.13]; $P < 0.001$). The lipid parameters, including TC, were significantly higher ($P < 0.001$) in the subgroup of patients receiving lipid medications who were totally nonadherent to these medications (TC 4.4 mmol/L [±0.9 mmol/L]) versus those who were totally adherent to their lipid medications (TC 3.8 mmol/L [±0.7 mmol/L]) (Supplementary Table 1).

There was a trend toward higher mean HbA_{1c} values in those patients totally nonadherent to OHAs (HbA_{1c} 8.2% (±2.4%)] versus those partially nonadherent to OHAs (HbA_{1c} 8.0% [±2.1%]; P = 0.088) (Supplementary Table 2).

CONCLUSIONS

The difficulty in diagnosing medication adherence reliably in a clinically useful manner remains a major unmet clinical need (4,5,8). This study shows for the first time that a routine urine sample collected in the primary care setting for urine microalbumin screening at the time of annual review can be used to objectively detect, using LC-MS/MS, nonadherence to treatment in people with T2DM. Anecdotally, the test is well accepted by patients and helps to initiate a discussion about the reasons for nonadherence and ways to overcome them (9).

Further, we confirm that there are high rates of nonadherence in people with T2DM within a primary care setting, as demonstrated previously (3). The study also demonstrates that nonadherence is associated with poor control of diabetes and lipids. Since biochemical nonadherence testing indicates only short-term nonadherence, the higher HbA_{1c} levels in the nonadherent population compared with the adherent population provides preliminary evidence that the test may

Table 1—Demographics and clinical and biochemical characteristics of adherent and nonadherent patients as detected by urine LC-MS/MS screen in patients with T2DM attending primary care

	All patients	Total adherent	Any nonadherent (total + partially nonadherent)	Total nonadherent	*P* value£	*P* value†
Number	228	164 (71.9)	64 (28.1)	13 (5.7)		
Age, years	59.9 (12.6)	60.3 (12.7)	59.1 (12.4)	47.3 (11.6)	1.1 (0.555)	12.9 (<0.001)
Male	123 (53.9)	91 (55.5)	32 (50.0)	7 (53.8)	0.455	0.721
Prescribed medications$	4 (3–6)	4 (2–6)	5 (3–6)	3 (2–4)	−1 (0.262)	1 (0.187)
Screened medications$	3 (2–4)	3 (2–4)	4 (3–6)	2 (1–3)	−1 (0.043)	1 (0.323)
Detected medications$	3 (2–4)	3 (2–4)	2 (1–4)	0	1 (0.026)	3 (0.005)
HbA_{1c}, %	7.21 (1.3)	7.0 (1.0)	7.7 (1.8)	8.3 (2.6)	−0.7 (0.001)	−1.0 (0.008)
HbA_{1c}, mmol/mol	55.1 (15.0)	53.2 (11.41)	59.9 (21.0)	63.0 (32.9)	6.3 (0.004)	−6.2 (0.143)
ACR, mg/mmol	8.5 (26.3)	4.7 (11.6)	18.1 (44.8)	22.2 (45.9)	−13.8 (0.001)	−18.4 (0.001)
TC, mmol/L	4.0 (1.0)	3.8 (0.7)	4.4 (1.6)	5.7 (3.0)	−0.5 (0.001)	−1.7 (<0.001)
LDL-C, mmol/L	2.1 (0.6)	2.1 (0.5)	2.3 (0.7)	2.7 (0.9)	−0.3 (0.004)	−0.6 (0.004)
HDL-C, mmol/L	1.4 (2.7)	1.3 (1.2)	1.8 (4.9)	1.0 (0.3)	−0.5 (0.248)	0.21 (0.620)
TC/HDL ratio	3.5 (1.0)	3.8 (0.7)	3.9 (1.1)	5.1 (1.1)	−0.6 (<0.001)	−1.5 (<0.001)

Values are expressed as *n* (%) for age and sex, median (interquartile range), or mean (SD) unless otherwise indicated. Any nonadherent, patients who were either partially or totally nonadherent to all prescribed cardiovascular medications; LDL-C, LDL cholesterol; Total adherent, detection of all prescribed cardiovascular medications; Total nonadherent, patients in whom none of the prescribed cardiovascular medications were detected. £Difference in the mean or median between total adherent and any (total and partial) nonadherent patients. †Difference in mean or median between total adherent and total nonadherent patients. $Average number of medications in each case with the range in parentheses. Independent *t* test was used to compare the means of ages. A Mann-Whitney *U* test was used to compare the median number of drugs prescribed, screened for, and detected. ANCOVA was used to adjust for age and sex when comparing the means of ACR, HbA_{1c}, and lipid profile (difference is based on estimated marginal means using the Bonferroni method for CI adjustment).

predict longer-term nonadherent behavior. More research is needed to confirm whether biochemical testing is a predictor of longer-term outcomes. Furthermore, adherence is a complex, dynamic process, and whether biochemical adherence testing induces a change in behaviour needs to be confirmed.

Previously, in a study of ~1,400 patients with hypertension, it was noted that for every increase in the number of prescribed antihypertensive agents the risk for nonadherence (as detected using biochemical screening) increases by 80% (10). In this current primary care study, we did not find any significant association between the total number of prescribed medications and mean HbA_{1c} values or mean lipid values. Larger studies may help to establish whether there is a threshold of OHAs and cardiovascular disease medications that increases the risk of nonadherence in people with T2DM.

Interestingly, the study also shows that rates of nonadherence to statins are much higher. We speculate that the reasons for this may include side effects such as myalgia or the poor perception of statins in the general population (11). The precise knowledge about nonadherence to a specific medication can help to tailor nonadherence advice, which is important to formulate an effective intervention that improves adherence to treatment (8).

Our study had several limitations. Our results are based on a small observational study, and future larger studies are required to confirm these preliminary findings. We also recognize the unavailability of a second measure of adherence, such as patient self-reported measures or prescription refill rates, for comparison in this study or of any data on barriers to nonadherence. Finally, our study is not protected from the so-called "toothbrush effect," where patients may have taken their medications just a few days before follow-up in general practice (12). Thus, the spot urine assay may have underestimated nonadherence.

In conclusion, a single urine spot sample can be used to objectively screen for nonadherence in primary care, and the technique demonstrates that nonadherence to cardiovascular therapies is high in people with T2DM attending primary care. This could be used to inform clinical decisions about treatment alteration and to improve patient outcomes.

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References

1. American Diabetes Association. 8. Cardiovascular disease and risk management: *Standards of Medical Care in Diabetes—2015*. Diabetes Care 2015;38(Suppl.):S49–S57

2. Khunti K, Kosiborod M, Ray KK. Legacy benefits of blood glucose, blood pressure and lipid control in individuals with diabetes and cardiovascular disease: time to overcome multifactorial therapeutic inertia? Diabetes Obes Metab 2018;20:1337–1341

3. Egede LE, Gebregziabher M, Dismuke CE, et al. Medication nonadherence in diabetes: longitudinal effects on costs and potential cost savings from improvement. Diabetes Care 2012;35:2533–2539

4. Khunti K, Seidu S, Kunutsor S, Davies M. Association between adherence to pharmacotherapy and outcomes in type 2 diabetes: a meta-analysis. Diabetes Care 2017;40:1588–1596

5. Clifford S, Perez-Nieves M, Skalicky AM, Reaney M, Coyne KS. A systematic literature review of methodologies used to assess medication adherence in patients with diabetes. Curr Med Res Opin 2014;30:1071–1085

6. Tomaszewski M, White C, Patel P, et al. High rates of non-adherence to antihypertensive treatment revealed by high-performance liquid chromatography-tandem mass spectrometry (HP LC-MS/MS) urine analysis. Heart 2014;100:855–861

7. Moffat A, Osselton D, Widdop B, Watts J. *Clarke's Analysis of Drugs and Poisons*. 4th ed. London, U.K., Pharmaceutical Press, 2011

8. Nieuwlaat R, Wilczynski N, Navarro T, et al. Interventions for enhancing medication adherence. Cochrane Database Syst Rev 2014;11:CD000011

9. Gupta P, Patel P, Horne R, Buchanan H, Williams B, Tomaszewski M. How to screen for non-adherence to antihypertensive therapy. Curr Hypertens Rep 2016;18:89

10. Gupta P, Patel P, Štrauch B, et al. Risk factors for nonadherence to antihypertensive treatment. Hypertension 2017;69:1113–1120

11. Matthews A, Herrett E, Gasparrini A, et al. Impact of statin related media coverage on use of statins: interrupted time series analysis with UK primary care data. BMJ 2016;353:i3283

12. Chatterjee JS. From compliance to concordance in diabetes. J Med Ethics 2006;32:507–510